



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

09/103,745

06/24/1998

SUDHIR AGRAWAL

IDRA-740US1

3401

32254 7590 02/12/2008

KEOWN & ZUCCHERO, LLP
500 WEST CUMMINGS PARK
SUITE 1200
WOBURN, MA 01801

EXAMINER

WOLLENBERGER, LOUIS V

ART UNIT

PAPER NUMBER

1635

MAIL DATE

DELIVERY MODE

02/12/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 09/103,745	Applicant(s) AGRAWAL, SUDHIR	
	Examiner LOUIS V. WOLLENBERGER	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 December 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-5 and 16-18 is/are pending in the application.
- 4a) Of the above claim(s) 3-5 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 16-18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 9/10/2007 has been entered.

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 12/13/2007 is acknowledged. The traversal is on the ground(s) the claims now pending are essentially identical to those pending since 11/3/2004, which claims have undergone substantive examination without restriction to date. Applicant's arguments are found persuasive in part. The Requirement as applied to Groups I and III is hereby withdrawn. Claims 16-18 are rejoined with Claim 1 for prosecution on the merits, as the subject matter substantially overlaps and no undue burden is present. The Requirement as applied between Group II and I/III, however, is maintained for the reasons set forth in the Requirement. With Applicant's amendment of 9/10/07, Claims 3-5 no longer overlap in scope with the composition of claim 1 or methods claims 16-18. While it may be true the claims remained essentially unchanged since 2004, the Markush style of claiming has not required the Examiner to search each embodiment to conduct a full and proper examination of the claims, nor is the examination to date an admission by the Office that each alternative member of the Markush has been searched and examined. As Applicant knows, prior art that teaches one member of the Markush is sufficient to anticipate the claim as a whole. The prosecution history to date clearly shows the Office has searched and considered the compositions and methods drawn to the 2'-O substituted CpG containing phosphorothioate oligonucleotide embodiment. Thus, while alternative embodiments have always been present for the Examiner to consider, the Examiner has never been required to consider these alternative embodiments to reject the claims, and there is no disclosure of record to indicate any of these alternative embodiments has received substantive examination. Therefore, no burden has been present to date. However, with the separation of the individual members of the Markush into

Art Unit: 1635

separate independent claims, as in the amendment of 9/10/07, a burden has become apparent to this Examiner, since the Examiner is now forced to search and examine not only the 2'-O-substituted embodiment but at least one other type of CpG modification, recited in claims 3-5, each of which is distinct from and not specifically required by any of claims 1 or 16-18. Moreover, there is nothing to prevent applicant from further separating the members of the Markush group of claims 3-5 into additional independent claims, which would further aggravate the burden of examination.

However, while the Restriction is maintained, Applicant is invited to submit a generic linking claim, linking the inventions of Groups I and I/III. In the presence of a linking claim, the restriction requirement among the linked inventions would be **subject to** the nonallowance of the linking claim(s). Upon the indication of allowability of the linking claim(s), the restriction requirement as to the linked inventions **would** be withdrawn and any claim(s) depending from or otherwise requiring all the limitations of the allowable linking claim(s) rejoined and fully examined for patentability in accordance with 37 CFR 1.104 **Claims that require all the limitations of an allowable linking claim** would be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

Applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, the allowable linking claim, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Therefore, the requirement as applied between Group II and Groups I/III (now rejoined) is still deemed proper and is therefore made FINAL.

Status of Application/Amendment/Claims

Applicant's response filed 9/10/2007 to the Final Rejection mailed 4/13/2007 is considered herein. Rejections and/or objections not reiterated from the previous office action mailed 4/13/2007 are hereby withdrawn. The following rejections and/or objections are either

Art Unit: 1635

newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 12/13/07, claims 1, 3–5, and 16-18 are pending. Claims 3-5 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/13/07.

Claims 1 and 16-18 are examined herein.

Claim Rejections - 35 USC § 102—withdrawn

The rejection of Claim 1 under 35 U.S.C. 102(b) as being anticipated by Cook (U. S. Patent Number 5,212,295) is withdrawn in view of Applicant's amendment to claim 1 ("consisting of"). Cook does not specifically teach a modified phosphorothioate antisense oligonucleotide wherein the modification specifically consists of a 2'-O-substituted CpG.

Claim Rejections - 35 USC § 102—withdrawn

The rejection of Claim 1 under 35 U.S.C. 102(b) as being anticipated by Agrawal et al. (WO 94/01550) is withdrawn in view of Applicant's amendment to the claim ("consisting of") for the reasons discussed above under Cook.

Claim Rejections - 35 USC § 102—withdrawn

The rejection of Claim 1 under 35 U.S.C. 102(b) as being anticipated by Kawasaki et al. (1993) *J. Med. Chem.* 36:831–841 is withdrawn in view of Applicant's amendment to the claim ("consisting of").

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Art Unit: 1635

Claims 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of reducing the side effects of antisense phosphorothioates having one CpG dinucleotide by modifying the CpG with a 2'-O substitution, does not reasonably provide enablement for methods of reducing the side effects of antisense phosphorothioates having multiple (i.e., two or more) CpG dinucleotides by modification of only one CpG.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

Claim interpretation:

With entry of the amendment filed 9/10/07 and 12/13/07, introducing the limitation "consists of," the claims are considered to be limited to phosphorothioate oligonucleotides containing as the only other modification a single 2'-O substituted CpG. A 2'-O-substituted CpG

Art Unit: 1635

is considered to embrace single and double incorporation of a 2'-O moiety into either the cytidine, guanine, or both of said CpG, consistent with the definition given at paragraph 25 of the instant pre-grant application publication (US 20030036516 A1). The specification defines the term "phosphorothioate oligonucleotide" as an oligonucleotide containing at least one phosphorothioate internucleoside linkage (paragraph 20).

The instant claims place no restriction or specific requirements on the position of the modified CpG dinucleotide relative to the 5' or 3' termini of the antisense. Thus, the claims embrace phosphorothioate antisense oligos consisting of a single 2'-O substituted CpG at any position in the oligo. The claims place no restriction on the length or nucleotide sequence of said oligonucleotide. Thus, the claims embrace any phosphorothioate antisense oligonucleotide to any target site.

The rejection:

Pre- and Post-filing art teaches the substitution of deoxynucleotides in a CpG dinucleotide with 2'-O-methylribonucleotides impairs the natural recognition of CpG dinucleotides by the receptors in the immunostimulatory pathway and the subsequent downstream immune responses such as B-cell proliferation and cytokine induction (Agrawal et al., 2001 *Curr. Cancer Drug Targets* 1:197-209, page 203; and Zhao et al., 1996 *Biochem. Pharmacol.* 51:173-182). However, the studies and exemplary data specifically shown in the pre- and post-filing for reducing the immunostimulatory properties of CpG containing oligonucleotides by chemical modification show only that the modification of each CpG in an oligonucleotide having one or more CpGs reduces immunostimulation. The Examiner fails to find adequate representation in the pre- or post-filing art or the specification that modification of only one CpG in an antisense having multiple CpGs reduces immunostimulation, as required by the instant claims. The extrinsic and intrinsic data shows only that complete modification of each CpG in a CpG-containing, antisense phosphorothioate eliminates or reduces the non-specific immunostimulatory effects of the oligonucleotide. There are no working examples directed to the embodiments specifically claimed.

Therefore, in view of the mechanism by which CpG containing oligonucleotides trigger immunostimulation, there is reason to believe antisense oligos having multiple unmodified CpGs in addition to a single modified CpG would continue to bind to cellular receptors and stimulate

Art Unit: 1635

the immune system despite the presence of a single modified CpG. Stated another way, there is insufficient evidence to show the modification of only one CpG in an antisense phosphorothioate having more than one CpG would reduce the side effects of the antisense in vivo. Thus, there is sufficient evidence to doubt whether the claimed oligonucleotides will provide for the effects recited in the claims. Thus, at the time of filing, neither the specification nor the prior art had shown that modification of a single CpG in an antisense having multiple CpGs is sufficient to produce each of the effects recited in the claims. A nexus correlating the reduction or loss of immunostimulatory activity with the modification of a single CpG in an antisense phosphorothioate having more than one CpG is not found in the pre- or post-filing art or the instant specification.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Claim Rejections - 35 USC § 103

Claims 1 and 16-18 rejected under 35 U.S.C. 103(a) as being unpatentable over Cook (U.S. Patent Number 5,212,295); Cook et al. (U.S. Patent 5,670,633); and Metelev et al. (U.S. Patent 6,143,881).

Claim interpretation:

The claims are interpreted as above in the rejection under 35 USC 112.

The rejection:

The Examiner recognizes Applicant has discovered the immunostimulatory properties of CpG-containing oligonucleotides may be reduced by chemical modifying the CpG units within the oligonucleotide. Modifications include 2'-O substitutions of the cytidine, guanidine, or both.

While the prior art does not teach chemically modifying the 2' positions of CpGs to reduce the non-specific effects triggered by such oligonucleotides, the prior art, nevertheless, clearly taught that 2'-O-alkyl substitutions may be used to protect phosphorothioate oligonucleotides from nuclease-catalyzed degradation. More specifically, the prior art taught that

Art Unit: 1635

as few as one or two 2'-O-methyl substituted nucleotides may further enhance the nuclease resistance and pharmacokinetic properties of phosphorothioate antisense oligonucleotides. Given the prior art taught antisense oligonucleotides may be ~18-20 nucleotides in length, that any given antisense, depending on the target site, may comprise one or more CGs throughout the sequence, that the prior art generally recommends incorporating 2' substitutions at almost any position in an antisense to enhance nuclease resistance, and that the prior art recommends experimenting with the number and position of such modifications to optimize antisense activity, there is reason to question the patentability of the instant claims as one of skill following the direction and guidance in the prior art when designing an antisense to a particular target site would necessarily attempt to make and use a finite number of 2'-O-substituted PS oligonucleotides to the target site, wherein the number and position of the 2'-substitution would be varied to obtain an optimally active antisense against that target site. Any C, G, A, and/or T nucleotide therein could be modified during the course of this routine optimization. If one or more 2'-O substitutions were incorporated into the C or G or both of a CG sequence in an oligo, the practitioner would expect to obtain the benefits disclosed by the prior art, but would also unknowingly obtain the properties inherent to such oligonucleotides, including those effects discovered by Applicant, recited in the preambles of the instant claims. Further, the prior art suggests as few as one or two 2'-O substitutions may be sufficient to increase nuclease resistance. Therefore, the prior art suggests making and using phosphorothioate oligonucleotides having as few as one or two 2'-O-methyl modified nucleotides.

Cook (U.S. Patent Number 5,212,295) is relied on for the reasons of record. See Actions mailed 8/24/2005, 1/25/06, and 4/13/07.

While Cook does not teach confining 2'-O substitutions to CpG dinucleotides, Cook does teach phosphorothioate antisense oligonucleotides comprising one or more 2'-O substituted nucleotides for inhibiting gene expression in cells for research and therapeutic purposes. The disclosure reasonably suggests incorporating 2'-O substitutions into virtually any nucleotide at any position in any antisense phosphorothioate oligonucleotide for the utility and benefits disclosed therein, regardless of the sequence of the antisense. For example, at column 9, beginning at line 51, Cook states the phosphorothioated antisense oligonucleotides of their invention can be further improved "by making one or more substitutions or modifications to the

Art Unit: 1635

base or the sugar moieties of the individual nucleosides..."Preferred substitutions, listed at columns 6 and 12, include several types of 2'-O substitutions. Specific gene target sites recommended therein (col. 13) reasonably suggest that in many instances, antisense oligonucleotides may contain one or more CpG dinucleotides. It is therefore reasonable to infer from the disclosure of Cook that the sugars of neighboring cytidines and guanidines (i.e., CpGs) could be modified like any other A, T, C, or G nucleotide to obtain the benefits disclosed by Cook. Any phosphorothioated, CpG-containing antisense in which a 2'-O substitution is incorporated into either a cytidine or guanidine or both of a CpG sequence would necessarily be endowed with all properties inherent to such compounds, including those disclosed by Applicant. Therefore, Cook is considered to be relevant to the patentability of the instant claims, as Cook suggests making and using phosphorothioated antisense compounds containing one or more 2'-O-substituted nucleotides. The PS-containing, 2'-O-substituted oligos are recommended for in vivo applications in organisms and animals (cols. 12 and 13). As a result, one of skill would be motivated to apply the methodology of Cook when making any antisense oligonucleotide against any target to obtain the benefits taught by Cook (col. 9, for example).

It is not necessary for Cook to have taught or recognized the properties Applicant discloses to render such compounds unpatentable. Cook suggests making 2'-O substituted phosphorothioate oligonucleotides to any target. Were one of skill to prepare a compound according to Cook directed to a site comprising a single GpC sequence, such as that disclosed at Column 13 of Cook, and were one of skill, during the course of routine optimization, to place the 2'-O substitution on the C and/or G nucleotide of the antisense, one would necessarily obtain all of the benefits disclosed by Applicant, though motivated for the purpose of obtaining the benefits taught by Cook. It is fundamental that properties inherent to suggested compounds are disclosed along with the compounds themselves. "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." See MPEP §2112.

Nevertheless, Cook does not stand alone in the prior art as the only disclosure teaching and recommending phosphorothioate antisense oligonucleotides containing one or more 2'-O substitutions.

Cook (US 5,670,633) also teaches incorporating one or more 2' -O substitutions (col. 5) into phosphorothioate containing oligonucleotides to obtain one or more of the benefits disclosed therein at columns 5 and 8. Cook '633 further teaches that phosphorothioates may enhance the properties of sugar modified oligonucleotides, thereby recommending the combination of such modifications (col. 7, lines 25-30). Thus, Cook '633 echos and reinforces Cook '295.

Meteliev et al. expressly recommend making and using phosphorothioate oligonucleotides containing one or more 2'-substituted sugars (col. 5). The 2'-substituted ribonucleotides can be present singly, in pairs, or in larger contiguous segments (col. 5, lines 44-46). Preferred 2'-substitutions include the 2'-O substitutions listed at column 5. In one example, it is said 2'-OMe ribonucleotides in an oligonucleotide phosphorothioate enhance resistance to exonucleolytic digestion (col. 10). Specifically claimed are hybrid antisense oligonucleotides complementary to a target nucleic acid, comprising one or more phosphorothioates and at least two 2'-O-methyl substituted ribonucleotides (claim 1). Applicant's claims embrace instances wherein both the C and G are substituted, and therefore PS oligos having two 2'-O-substituted nucleotides, albeit specifically at the C and G of the CG sequence. Meteliev et al. further recognize that PS and 2'-substitutions constitute result-effective parameters, stating "The ability to vary the numbers and positions of phosphorothioate and/or phosphorodithioate internucleotide linkages, deoxyribonucleotides, and ribonucleotides or 2'-substituted ribonucleotides allows the investigator to examine in detail how each of these variables affects the parameters of nuclease resistance, duplex stability and RNase H activation" (col. 5, lines 55-61).

Thus, there is substantial direction and guidance in the prior art motivating one of skill to make and use phosphorothioate antisense oligonucleotides containing one or more 2'-O substituted nucleotides at almost any position for inhibiting virtually any known gene. While the prior art does not specifically recommend modifying the Cs and Gs in a CpG sequence within an oligonucleotide, one of skill following the general direction and guidance of the prior art would inevitably make and use a variety of antisense PS-containing, 2'-O substituted oligonucleotides

Art Unit: 1635

against a wide variety of sequences, which in many instances may be expected to comprise one or more CpG dinucleotides.

The prior art is replete with disclosures recommending specific target sites for antisense-mediated knockdown. Many contain one or more GC sequences necessitating an antisense with one or more CpGs. Thus, during the course of routine optimization, one of skill would inevitably make and use a finite number of PS antisense oligonucleotides comprising one or more 2'-O substitutions. For example, Cook '295 recommends targeting the sequence TTG CTT CCA TCT TCC TCG TC to inhibit papilloma virus (col. 13). The site, just 20 nucleotides in length, contains a single CG sequence near the 3' terminus. Thus, a potential antisense targeting this site would comprise a single CpG sequence near the 5' end. One of skill seeking to use 2'-O-substituted PS antisense oligonucleotides having optimal activity against this site, according to the method of Cook (both patents) and Metelev et al. would be expected to make a finite number of PS oligonucleotides having one or more 2'-O substitutions at different regions throughout the molecule, including the Cs and Gs therein. If one were to follow the invention specifically disclosed by Metelev et al., one would test 2' substitutions singly or in pairs at various positions throughout the antisense, and would reasonably be expected to prepare and use a molecule embraced by the instant claims. Moreover, one of skill apprised of the disclosures of each of the references cited herein would immediately envision the finite set of PS-containing 2'-O substituted antisense molecules complementary to the papilloma virus site recommended by Cook '295. It would be obvious to attempt to make and use each one of those to identify those having optimal stability and activity. Thus, molecules embraced by the instant claims would reasonably be made and used during the course of routine optimization against the papilloma virus site. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Suggestion, teaching, or motivation to combine the relevant prior art teachings to achieve an embodiment within the claimed invention does not have to be found explicitly in the prior art references sought to be combined, but may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself (*Dystar*, 464 F.3d at 1361; see also *Pfizer Inc. v. Apotex Inc.*, 82 USPQ2d 1321 (Fed. Cir. 2007). In the instant

Art Unit: 1635

case one of skill, charged with the knowledge of the prior art, including each of the references cited herein, would have known the benefits obtainable by the incorporation of one or more 2'-O substitutions into a phosphorothioate antisense. Optimizing antisense activity against any particular target site, such as the papilloma site recommended by Cook, would have involved nothing more than routine testing of a finite number of oligonucleotides, with a reasonable expectation of success based on the guidance in the prior art.

Accordingly, in the absent of convincing evidence to the contrary, the instantly claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LOUIS V. WOLLENBERGER whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/

Examiner, AU1635

February 2, 2008